Decision Memo for Actinic Keratoses (CAG-00049N)

Decision Summary

The Coverage Issues Manual will be revised to indicate that Medicare will cover the destruction of actinic keratosis, without restrictions based on lesion or patient characteristics, using surgical or medical treatment methods, including but not limited to:

- cryosurgery with liquid nitrogen,
- curettage,
- excision, and
- photodynamic therapy.

CMS expects that practitioners will maintain sufficient information, as required under 42 CFR § 424.5(a)(6), to enable them to demonstrate entitlement to Medicare reimbursement for covered procedures and services.

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Decision Memo

(The information contained here represents only the first step towards making coverage of these services effective. A manual instruction must be prepared and approved, and the necessary billing and claims processing instructions must be prepared. In addition, changes must be made to bill processing systems in order to allow payment to be made. Consequently, the effective date of service will not be known until the manual instruction has completed the clearance process and been assigned an effective date.)

TO: Administrative File CAG-00049N: Management of Actinic Keratosis

FROM:

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SUBJECT: National Coverage Determination

DATE: July 19, 2001

This memo serves four purposes: (1) describes actinic keratosis (AK) and methods of managing this skin lesion; (2) reviews the history of Medicare's coverage of management of actinic keratosis and provides a timeline of recent activities; (3) presents and analyzes the relevant scientific and clinical data related to actinic keratosis; and (4) delineates the reasons for making a positive national coverage decision.

Clinical Background

Actinic keratoses (AKs), also known as solar keratoses, are common, sun-induced pre-cancerous skin lesions that are confined to the epidermis. The lesions typically appear as circumscribed, rough, scaly patches on sun exposed skin, ranging from flesh-colored to reddish-brown. Due to their distinctive roughened quality, AKs may be easier to detect by palpation than visualization (especially in the early stages of development). AKs are usually 1 to 3 mm in diameter, but may be larger in size and may appear in clusters.

AKs are dynamic in nature. Although most AKs are asymptomatic, some may exhibit signs and symptoms such as thickening, burning, tenderness, or itching. AKs may also progress to squamous cell carcinoma (SCC), a form of skin cancer. This progression may or may not be related to the development of signs and symptoms, and the scientific evidence related to AK progression is discussed more thoroughly in the Summary of Evidence section of this document. Finally, AKs can also regress. In two studies, the rates of AK regression were 21% and 25.9% a year. In a third study, rates of regression were reported for prevalent and incident AKs. Prevalent AKs (those that were present on the first examination) exhibited a regression rate of 74% while incident AKs (those developing following the initial examination) regressed only 29% of the time. Over the course of one year, however, 15% of AKs that regressed were found to later recur. This raises concern that the regressed AK may still be present, but not appreciable on examination.

AKs are most prevalent in fair-skinned individuals with a history of significant sun exposure. The prevalence of AKs increases with advancing age, and AKs are more common in men than women. AKs are more common in immunosuppressed patients and in patients with some genetic disorders (such as xeroderma pigmentosum). In five studies on AK (using either a random or a population-based sample), the overall reported prevalence of AKs ranged from 23-61.1%3. In these studies, the reported annual incidence of AK ranged from 12.6-43.4%4. These rates of prevalence and incidence demonstrate a clear relationship to geographic location, as the lower rates were reported from a study conducted in Wales and the higher rates reported from several studies in Australia. Due to these high rates of prevalence and incidence, destruction of AKs is the most commonly performed outpatient dermatologic procedure in the United States5.

The available literature on AK suggests that this issue is particularly relevant to the Medicare population. Frost, et al. (2000) reported 83% prevalence of AKs in Australian men aged 60-69 years. However, this reported prevalence rate is impacted by geographic region, as sun exposure in the Australian population is likely higher than most areas in the United States.

A search of Medicare data by the Oregon Health & Science University (OHSU) indicated that 6.7-9.1% of beneficiaries over age 65 were treated for AKs between 1991 and 1995_{-}^6 . These treatment percentages are likely lower than the actual prevalence of AKs in the Medicare population, as OHSU reports that "...only a small proportion of individuals with AKs seek or receive treatment".

Management Options

Various options exist for managing AKs, and clinicians may consider several factors to determine the most appropriate management strategy, including size, location or growth pattern of the lesion, patient preference, and patient medical history. Common treatments for AK include cryosurgery with liquid nitrogen, topical treatments, and curettage. Other less common treatments for AK include dermabrasion, excision, chemical peels, laser therapy, and photodynamic therapy (PDT)⁸. An alternative approach to the management of AKs is watchful waiting, such that lesions are removed only when they exhibit specific clinical features suggesting possible transformation to invasive SCC.

Cryosurgery with liquid nitrogen, the most common treatment for AKs in the U.S., is most appropriate when discrete AKs are present. With this procedure, liquid nitrogen is applied directly to AK lesions as a method of destruction. The procedure generally does not require the use of a local anesthetic and involves only mild pain and minor side effects, such as temporary post-procedural erythema.

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Topical treatments, such as the chemotherapeutic agent 5-fluorouracil (5-FU), are most commonly used for patients with multiple lesions. The 5-FU cream is applied to the entire region that is affected, and the recommended course of treatment involves several applications per day over a 2 to 4 week time span. 5-FU selectively targets the damaged skin, causing an inflammatory response with erythema, necrosis, and erosion. Numerous side effects are associated with 5-FU, including pain or irritation, tenderness, ulceration, burning, and inflammation. As a result, patient compliance is a significant concern with this treatment.

Curettage, which involves the use of a curette to scrape away the lesion, is another common method of treatment for AKs. In some instances, curettage may be used in combination with electrosurgery to stop bleeding or apply more damage to the affected area. The primary advantage of curettage is the ability to submit the specimen for histologic analysis, particularly in cases where invasive squamous cell carcinoma is suspected. Disadvantages of curettage include the need for local anesthesia and the potential for scarring.

Photodynamic therapy (PDT) represents an emerging technology in the treatment of AKs. PDT uses the topical agent 5-aminolevulinic acid (5-ALA) to selectively photosensitize the atypical cells of the AK lesion. Approximately 14 to 18 hours following application of the 5-ALA, the skin is exposed to a light source and the cells of the AK lesion are destroyed. Common side effects of PDT include erythema, stinging/burning, edema, and scaling or crusting of the lesion. The primary disadvantage of PDT is the need for treatment over a 2-day period.

FDA Approval

Each of the AK treatment options discussed in the previous section has received FDA approval. Since the 1960's, cryosurgery with liquid nitrogen has been routinely used for multiple medical indications. As a result, early clearance for cryosurgery was granted for general tissue destruction. In 1980, Cryomedics, Inc. received FDA clearance under the 510(K) process for the Krymed Liquid Nitrogen Cryojet, with destruction of AKs as a specific clinical indication (among several other dermatologic indications). Since 1980, there have been several additional cryosurgery devices cleared for dermatologic use.

In 1970, 5-FU (tradename Efudex®) was reviewed under the New Drug Application (NDA) process and determined to be safe and effective for the topical treatment of actinic or solar keratoses. Three different Efudex® products were approved for treatment of AKs: 2% fluorouracil topical solution, 5% fluorouracil topical solution and 5% fluorouracil topical cream. In October 2000, Dermik Labs received NDA approval for a generic 0.5% fluorouracil topical cream.

One PDT system currently has approval for the treatment of AKs. In 1999, DUSA Pharmaceuticals, Inc. received FDA approval for Levulan® KerastickTM. Levulan® KerastickTM involves the use of both a drug (20% ALA topical solution) and a device (the Levulan® KerastickTM for application of ALA and the BLU-UTM Illuminator as the light source). Levulan® KerastickTM received premarket approval (PMA) as a photodynamic therapy system "...for the treatment of non-hyperkeratotic actinic keratoses of the face or scalp" No other PDT system currently has FDA approval for the treatment of AKs.

History of Medicare's Coverage on AK Management

Presently, Medicare has no national policy with regard to the management of AK. In the absence of a national coverage policy on AK management, several Medicare contractors have developed local policies on AK and these local policies vary significantly.

Between 1998 and 1999, several contractors implemented local policies that limit removal of AKs to lesions that exhibit one or more of the following characteristics:

- are symptomatic and exhibit features suggestive of possible malignant transformation (e.g. bleeding, itching, pain, inflammation, notable change in size or color, etc.),
- are located on high risk anatomic sites (e.g., lips, ears, nose, eyelids, or a previous burn site),
- have failed to respond to topical chemotherapeutic agents, or
- occur in individuals with a high risk of malignant transformation (e.g. individuals with chronic immunosuppression, previous exposure to ultraviolet therapy, prior history of skin malignancy, prior exposure to arsenicals or radiation, etc).

Some other local policies, however, characterize AKs as precancerous lesions with the potential to progress to invasive SCC and allow routine treatment. In 2000, however, several of these policies limited the number of treatment sessions to four per year, unless further documentation is provided to justify additional treatments. Finally, some local contractors have no written policy on the treatment of AKs. In these instances, claims are subject to medical necessity determinations on a case by case basis.

Current Request

In December 1999, the Centers for Medicare & Medicaid Services (CMS), formerly known as the Health Care Financing Administration (HCFA), received a formal request for coverage consideration on treatment of AK from the American Academy of Dermatology Association (AADA). In January 2000, AADA representatives emphasized their concern regarding the inconsistencies that exist in various local medical policies on AK treatment. CMS offered to assist the AADA in working with the CMS Program Integrity Group to open a dialogue with various Medicare contractors in order to try to resolve some of the issues related to the treatment of AKs. In March 2000, CMS received a communication from the AADA requesting that their formal request for coverage consideration be placed on hold. In June 2000, CMS received a communication from the AADA requesting that the formal request be re-opened, thus beginning the formal coverage consideration process.

Timeline of Recent Activities

June Received a letter from the AADA requesting that CMS re-open their formal request.

6, 2000

August CMS notified the AADA that CMS has requested a technology assessment from the Agency for 15, Healthcare Research and Quality (AHRQ). 2000

May 8, Received technology assessment from AHRQ. 2001

May AADA representatives met with CMS to present additional information related to the findings of the technology assessment.

Summary of Evidence

Problem Formulation

In order to address the issue of managing AKs in the context of Medicare policy, CMS formulated the following questions:

1. Is there adequate evidence to support the routine removal of AKs in contrast to a strategy of watchful waiting?

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- 2. If #1 is YES, is there adequate evidence to select lesions for routine removal which have particular anatomic characteristics predisposing such lesions to SCC?
- 3. If #1 is YES, is there adequate evidence to select patients for routine removal of AKs who have certain high-risk characteristics predisposing them to SCC?
- 4. If #1 is YES, is there adequate evidence to demonstrate the differential efficacy of any particular treatment modalities?

Review of Evidence - Technology Assessment

In August 2000, CMS requested a technology assessment from the Agency for Healthcare Research and Quality (AHRQ) to review and assess the literature on incidence, treatment, and progression of AKs. AHRQ selected the Evidence-based Practice Center (EPC) at the Oregon Health & Science University (OHSU) to develop the evidence report. An EPC performs systematic reviews of the literature on a clinical topic to form evidence-based conclusions. Key questions for the technology assessment on AK, which are very similar to the above problem formulation questions, were developed by CMS, in consultation with AHRQ. Following a review by representatives of dermatologic professional societies, OHSU further refined the key questions and used them to guide development of the report. To view the key questions and final assessment for AK, see the attached Technology Assessment (PDF, 433KB).

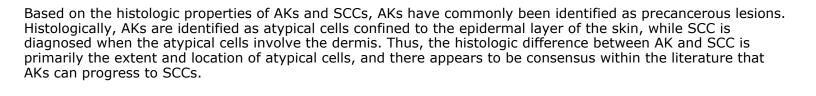
The conclusions of the technology assessment are described below, with supplemental analyses performed by CMS staff where pertinent, in the context of the key questions delineated above. The assessment did not address AKs on the lip, ear, eyelid, or in immunocompromised patients, as there is consensus that AKs should be removed routinely in these instances, due to relatively higher rates of progression to metastatic SCC¹⁰.

Question 1 - Is there adequate evidence to support the routine removal of AKs in contrast to a strategy of watchful waiting?

The argument supporting routine treatment of AKs relies upon the assumptions that:

- AKs are precancerous lesions,
- some AKs will progress to invasive SCC, and
- treating AKs will prevent development of invasive SCC.

Assumption 1 - AKs are precancerous lesions



The similarity between AK and SCC lesions is supported by studies examining the accuracy of clinical diagnoses of AK and SCC. Three studies reported in the technology assessment compared the clinical diagnosis of AK with pathologic results following a biopsy. The reported accuracy of clinical diagnosis ranged from 81-94% in these studies 11 . Two studies of interobserver agreement showed moderate to poor agreement on diagnosis of AK^{12} . One of these studies compared interobserver agreement between dermatologists while the other compared the diagnosis of a general practitioner to that of a dermatologist. Neither study submitted AK lesions for histopathological analysis to confirm clinical diagnoses.

Several studies indicated that the clinical diagnosis of SCC is less reliable than that of $AK_{\underline{13}}$. In one study, dermatologists correctly diagnosed SCC only 51% of the time, with surgeons and general practitioners demonstrating even lower diagnostic accuracy $\underline{14}$. In practice, AKs are frequently not subject to histopathological evaluation, but rather are treated on the basis of clinical examination alone.

However, a debate exists within the medical community over whether AKs should be identified as "precancerous lesions" or as "true cancers". Proponents of the view that AKs represent a true cancer argue that AKs and SCC represent a continuum, and that it is difficult, if not impossible, to distinguish when the "cancer" begins. Such proponents argue that the atypical cells presenting as an AK are indistinguishable from the atypical cells of SCC and also point to molecular similarities between AKs and SCCs, specifically the presence in both of a mutation of the p53 gene. This genetic link provides evidence that "...AK represents the beginning of the SCC continuum" 15.

In contrast, those who support the notion that AKs are a precancerous lesion emphasize the behavior of the lesion, noting that AKs frequently regress, do not grow actively, and do not have the potential to metastasize. They also note molecular similarities between AKs and sun-damaged skin without dysplasia.

Despite this ongoing dialogue regarding the nature of AKs as "precancerous" versus a "true cancer", there appears to be a consensus that AKs and SCCs are linked histologically. Further research is necessary to determine the specific mechanism of progression from an AK to invasive SCC and the malignant transformation of some SCCs.

Some evidence exists to support the assumption that some AKs will progress to SCC. As discussed earlier, AKs and SCCs are linked histologically, with the diagnostic difference existing mainly in location and degree of atypia of the cells. In addition, several studies have demonstrated that the presence of AKs is more strongly associated with the development of SCC than other factors, including age, gender, and skin type¹⁶.

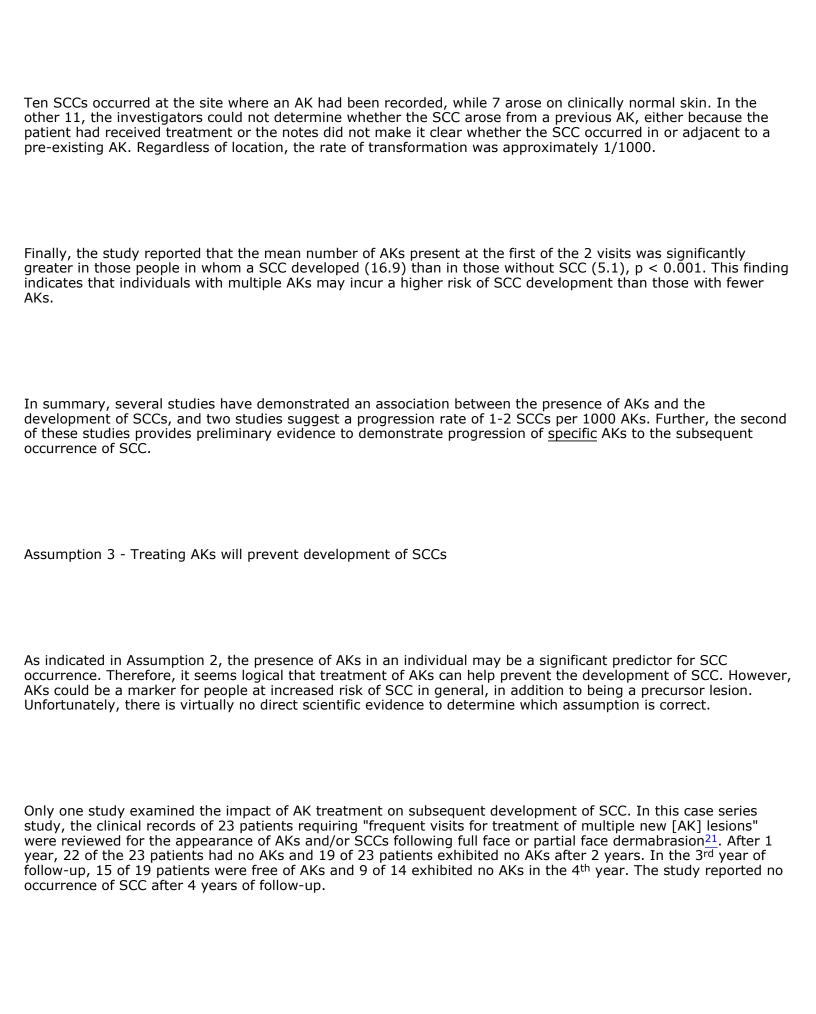
There are few sources of data to predict the rate of progression from AK to SCC. The technology assessment reported two well-conducted studies in Australia that reported a yearly progression rate of 1-2 SCCs per 1000 AKs¹⁷. However, only one of these two studies actually linked SCCs to a specific, pre-existing AK. CMS staff conducted a further analysis of these articles.

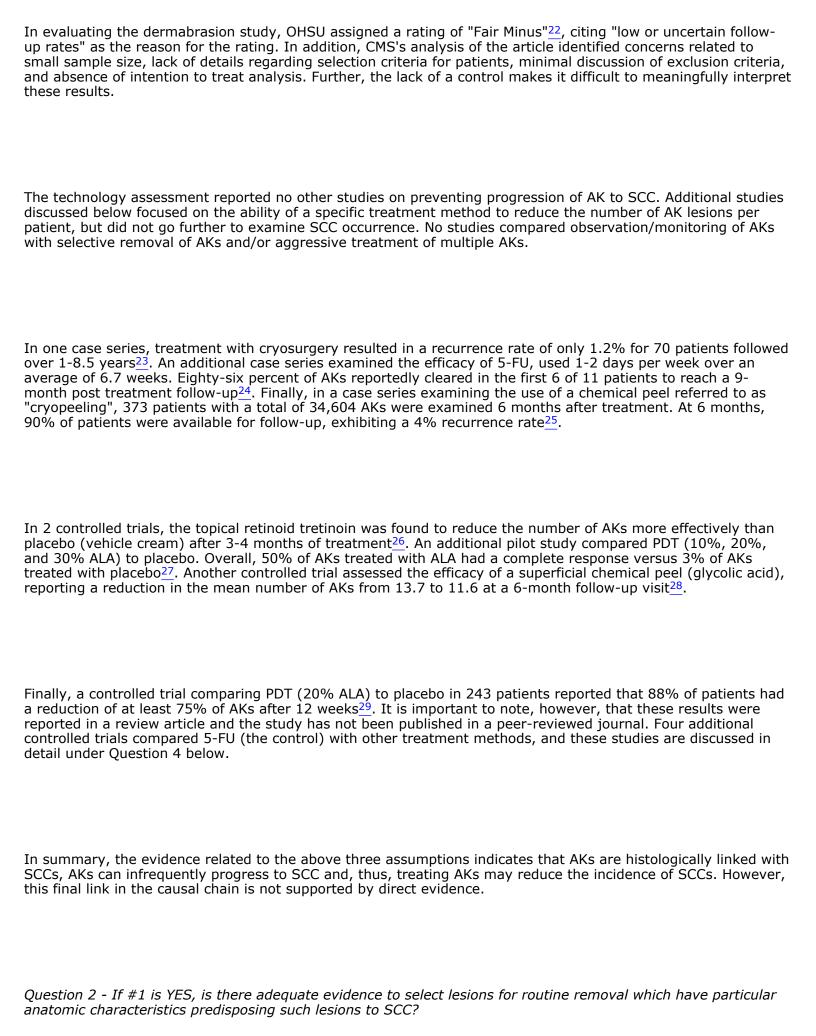
Both studies reported on a subset of a 5-year longitudinal study in Maryborough, a small Australian city. Investigators invited all residents of the city 40 years and older to attend an annual dermatological exam over a 5-year period.

In the first of these studies $\frac{18}{1}$, participants were examined by a team of experienced clinicians, and all clinically diagnosed AKs were noted. Participants were instructed that no AK treatment was necessary unless they noted lesion changes. 1,040 residents were examined in 1983, with a mean age of 58.8 years. On initial exam, 424 participants had no AKs (40.8%) and 616 (59.2%) had at least one. There were 4,746 AKs identified in the 616 participants with at least one AK (7.7 per person on average). During the course of the year, 3 of the 616 had lesions treated, thus 613 were available for analysis.

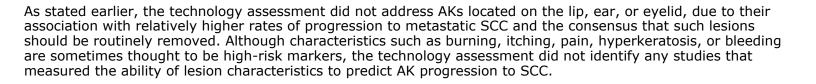
At the 1-year mark, 12 of 1037 participants ¹⁹/₂ developed a total of 14 SCCs. Of the 613 who had AKs and no treatment, 10 people developed a total of 11 SCCs (11 SCCs/613 participants, 1.8%). Of the 424 who had no initial AKs, 2 people developed a total of 3 SCCs (3 SCCs/424 participants, 0.7%). For every SCC that occurred, there were 429 AKs, resulting in an annual incidence rate for SCC of 0.24% for every lesion present at the first interview.

The second study represented a continuation of the Maryborough study discussed above, utilizing similar methodology $\frac{20}{20}$. However, this study attempted to grid specific AK lesions to measure specific patterns of progression. In this study, 1689 participants were seen on 2 consecutive years (4267 occasions) over the study period. On 2606 (61%) of these occasions, subjects exhibited at least one AK. On 28 separate occasions, a SCC had developed by the second visit (26 people).





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Question 3 - If #1 is YES, is there adequate evidence to select patients for routine removal who have certain high -risk characteristics predisposing them to SCC?

The technology assessment also did not address AKs occurring in immunocompromised patients (such as transplant patients). Again, this was based on the consensus that AKs should be removed routinely in these patients due to a relatively higher risk of progression to metastatic SCC. Beyond this patient category, prior patient history of skin cancer has also been linked with a higher likelihood of subsequent SCC occurrence. The technology assessment identified one large, prospective, randomized trial that examined the use of retinol to prevent skin cancer. In this study of 2297 Arizona residents who had at least 11 AKs, the strongest risk factor for developing SCC was a prior history of skin cancer 30.

Question 4 - If #1 is YES, is there adequate evidence to demonstrate the differential efficacy of any particular treatment modalities?

The studies in this section were included in the OHSU technology assessment, but were subjected to additional HCFA staff analysis. Four controlled trials have been conducted to compare 5-FU (the control) with other treatment methods. Bercovitch (1987) compared the use of 5% 5-FU with 5% 5-FU plus tretinoin cream in a double-blind, randomized trial. Twenty participants all had multiple AKs on the forearms and hands, and 5-FU was self-administered to both the forearms and hands twice daily. Following 5-FU application, .05% tretinoin cream was randomly applied to one side (treatment) and a placebo cream (control) to the other. The number of AKs were counted prior to treatment and at a 12-week follow-up session. Nineteen of the original twenty participants were available for assessment at the 12-week follow-up session.

This study reported a 78% reduction in AKs in the treatment side versus 73% reduction in AKs on the control side. Both responses were statistically significant at p < .04. The report also indicated a statistically significant difference between the 2 treatment responses, but the level of significance was not reported. There were several limitations with this study, including small sample size, lack of information on selection criteria (e.g., unclear use of consecutive patients), varying length of treatment per patient based on tolerance, lack of detailed information on blinding method, and lack of information on assessment of patient compliance with treatment.

Simmonds (1973) compared the effectiveness of 1% and 5% 5-FU in removing AKs on the face. Sixteen participants self-administered 1% 5-FU cream to the right side of the face and 5% 5-FU cream to the left side of the face, though participants and researchers were blinded to this distribution. Results of this study reported "...no difference in treatment time or degree of efficacy for either the 1% or 5% fluorouracil topical cream". Study limitations included small sample size, unclear criteria for judging response to treatment, and the omission of numerous methodological design characteristics (including selection criteria, clinical assessment criteria, etc.).

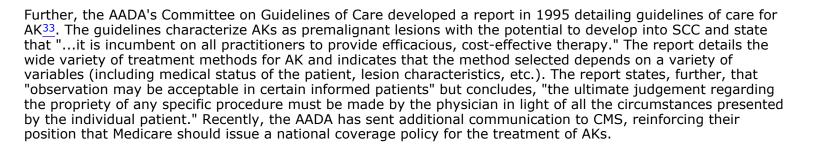
In 1999, Kurwa, et al. conducted a study to compare 5-FU (5%) to PDT (5-ALA followed by irradiation with a halogen lamp emitting red light). Seventeen patients with a long history of AKs on the forearms and hands were initially recruited for this study, and patients were randomized to apply 5-FU (twice daily for 3 weeks) to one hand and receive PDT to the other hand. Clinical margins of the AKs on both hands were traced prior to treatment and at 1 week, 4 weeks and 6 months following the start of treatment.

Fourteen of the original seventeen patients completed the study and the mean lesional areas were compared preand post-treatment. The study reported a mean lesional reduction of 70% for lesions treated with 5-FU and a 73% reduction in lesions treated with PDT after 6 months of follow-up. The difference in response to the two treatments was not statistically significant. No patients exhibited a complete destruction of AKs with either treatment. Limitations included small sample size, lack of information on selection criteria, lack of information on assessment of patient compliance with 5-FU, and non-blinding study design. Further, results at 1 and 4 weeks of follow-up were not reported.

A fourth study of 5-FU was reported in two different articles. Lawrence, et al. (1995) initially reported on a study comparing a medium-depth chemical peel (Jessner's solution and 35% trichloroacetic acid) to 5% 5-FU in 15 patients. Following a daily self-administration of 0.025% tretinoin cream to both sides of the face for 2 weeks, each patient was subjected to the chemical peel on the left side of the face and 5-FU to the right side of the face. AKs were counted prior to treatment and at 1, 6 and 12 months following treatment.

Twelve of the fifteen patients completed the 12-month study, and reported results indicate that "both fluorouracil [5-FU] and the chemical peel induced almost identical percent reductions (75%) in the number of AK". The study reports that this reduction in AKs was noted at the 1-month follow-up and persisted throughout the 12-month study period. As with earlier studies, methodological flaws included non-blinding study design, small sample size, lack on information on selection criteria and characteristics of the study setting, and a lack of information on whether patient compliance with 5-FU was assessed. Further, the results at 6 and 12 months of follow-up are confounded by intervening treatment of persistent AKs (35% trichloroacetic acid and cryosurgery at 6 months, shaving at 12 months).





The Skin Cancer Foundation

In 1998, The Skin Cancer Foundation submitted a letter to CMS indicating their objection to any "...proposed restrictions on the treatment of actinic keratoses by dermatologists." The letter further stated the position of The Skin Cancer Foundation that AKs evolve into skin cancer, but can be treated with little harm to the patient. The letter concluded that restricting the ability of the dermatologist to treat AK lesions is "entirely unjustifiable."

Additional Experts

The AADA's formal request for consideration, submitted to CMS, included over 50 letters from dermatology professors and department chairs at major universities and hospitals across the country. These letters all expressed the belief that AKs are premalignant lesions warranting routine treatment. Further, the letters urged CMS to implement a policy that does not place restrictions on treatment (based either on lesion characteristics, patient characteristics, or treatment type).

Other Countries

Finally, following a request from CMS, AHRQ searched an international database and found no other technology assessments on the management of AK. Given the high prevalence of AK in Australia, HCFA also reviewed Australian policy on the management of AK. Treatments for AK are covered by the Australian healthcare system, with NCDs on type of treatment left to the discretion of the physician.

CMS Analysis

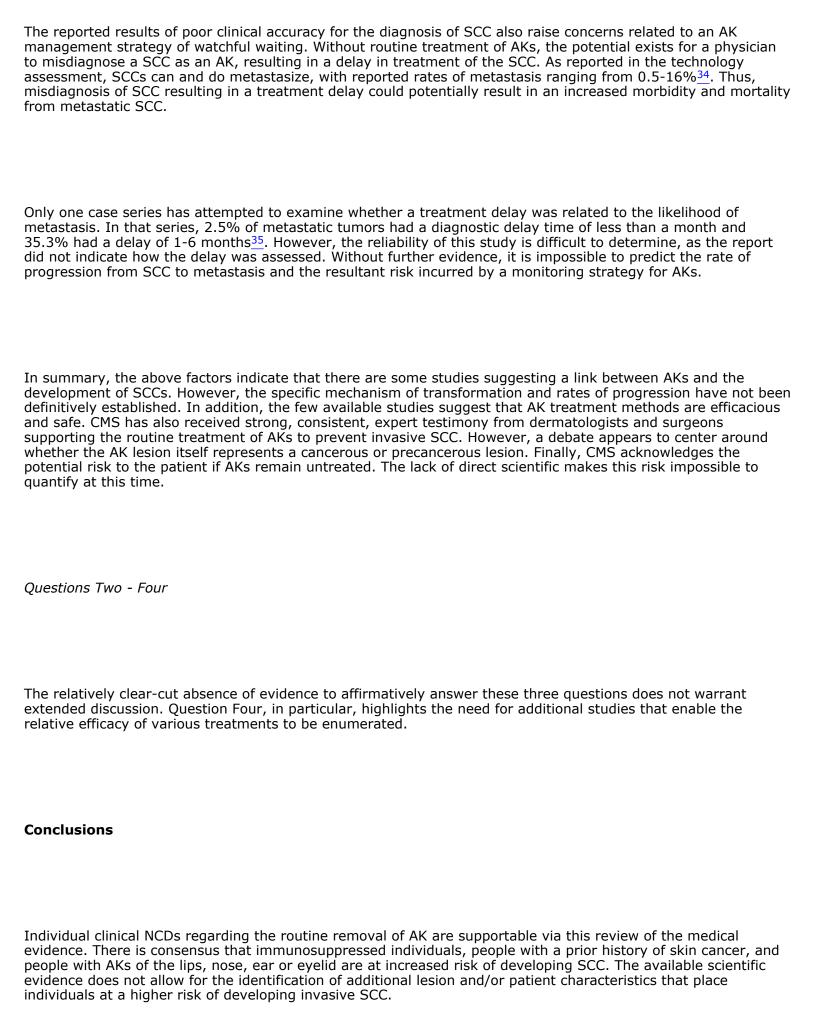
In addition to the technology assessment, this analysis takes into consideration the position statements of specialty societies, expert opinion of physicians, an internal review of Medicare utilization data, and all other information received by the agency on this topic. CMS also conducted an internal review of several articles included in the technology assessment, as well as additional articles submitted to the agency or identified through an internal literature search.

Question One

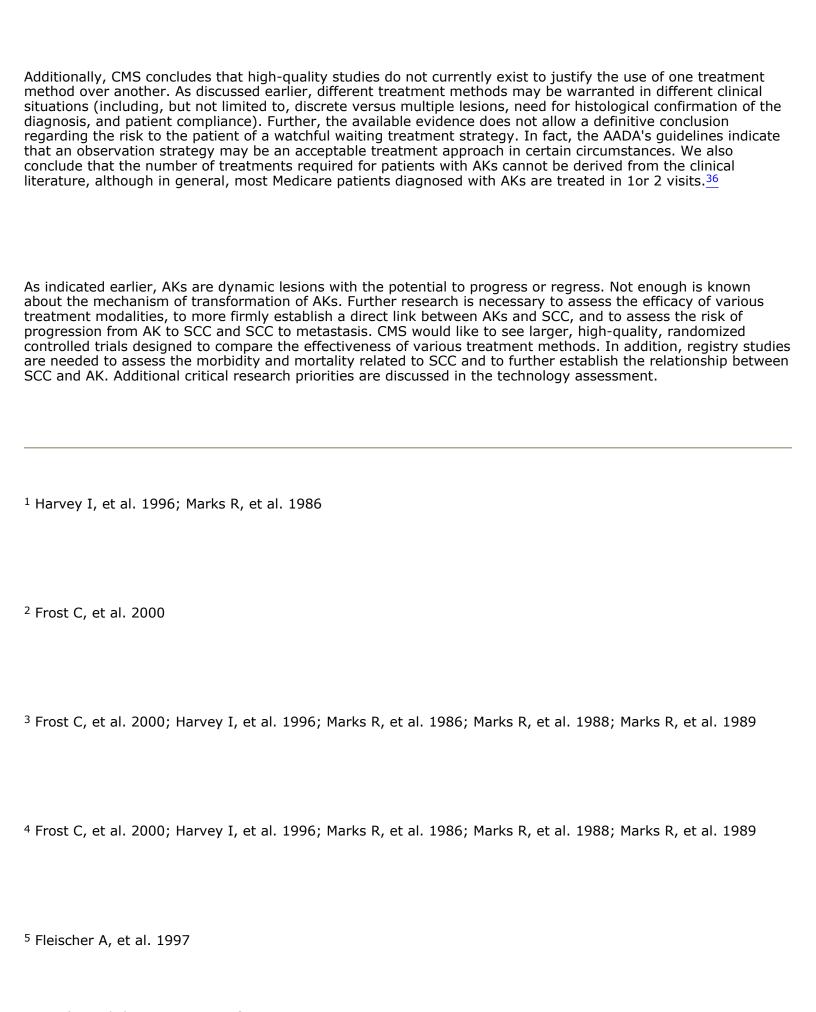
Overall, the body of **direct** scientific evidence to support routine treatment of AKs is small. Only one study has attempted to link the progression of specific AKs to the development of SCC, and only one case study on dermabrasion attempted to assess the impact of AK treatment on subsequent development of SCC. In addition, while a few studies have been conducted to examine the effectiveness of treatments in reducing the number of AKs, the studies tend to be small and are often case series. Further, the controlled trials that exist have not consistently included blinding, randomization and comparison of treatment methods to a placebo group. Despite these limitations, this small body of literature provides preliminary direct evidence indicating that AKs can progress to SCC and that treatment can reduce the number of AKs and possibly SCCs.

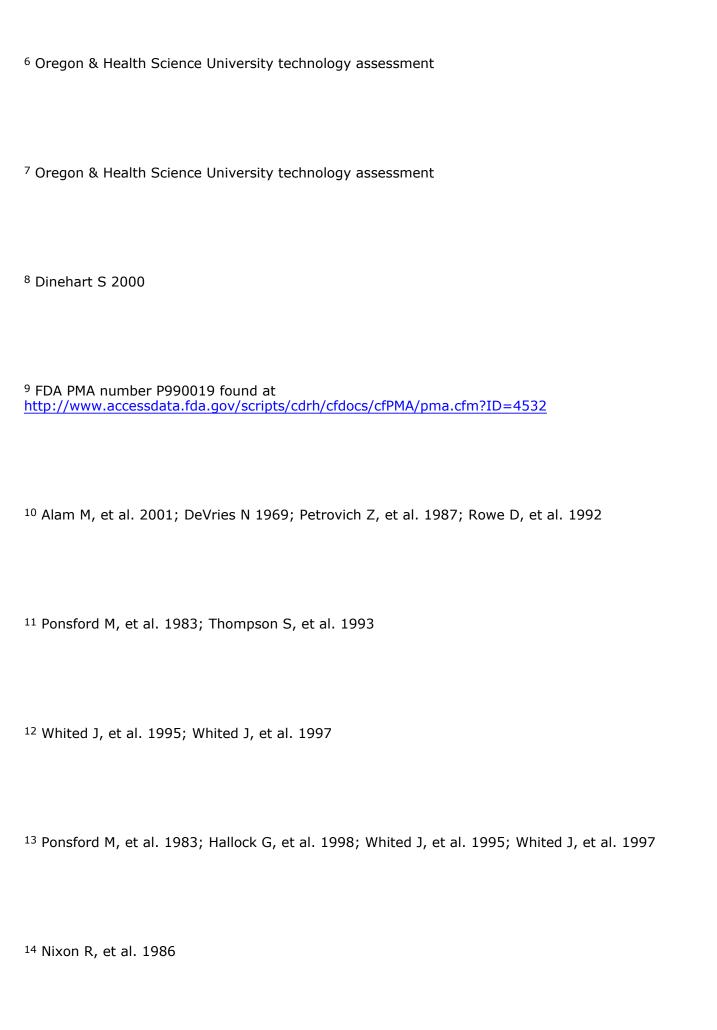
CMS has also taken into consideration several factors that offer **indirect** support for routine treatment. First, as discussed previously, several studies have demonstrated that the presence of AKs is more strongly associated with the development of SCC than most other factors. Based on this association of AKs and SCCs, CMS concludes that treatment of AKs may be warranted to prevent the risk of developing an invasive SCC.

Further, CMS concludes that the reported annual progression rates of 1-2 SCCs per 1000 AKs, when used to support a watchful waiting strategy for the treatment of AKs, may not reflect the actual long-term risk to the patient. With such a monitoring strategy, AK lesions that do not suggest the presence of malignant transformation would not be treated. Since it is likely that some of these asymptomatic lesions would endure in a given patient beyond 1 year, the reported annual rates of progression may not reflect a true risk to the patient. The true long-term risk to the patient is difficult to predict. Mathematical models reported in the technology assessment that attempt to extrapolate beyond an annual rate of progression contain several limitations, including assumptions of average number of lesions per patient and constant rates of progression.



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¹⁵ Leffell D 2000
¹⁶ Green A, et al. 1990; English D, et al. 1998; Marks R, et al. 1988
¹⁷ Marks R, et al. 1986; Marks R, et al. 1988
¹⁸ Marks R, et al. 1986
19 Final analysis excluded the 3 patients that received AK treatment during the study period.
²⁰ Marks R, et al. 1988
²¹ Coleman W 1996
²² To classify study quality, the OHSU technology assessment used criteria developed by the US Preventive Services Task Force (USPSTF). These criteria are presented in Appendix 2 of the technology assessment.
²³ Lubritz R, et al. 1982

